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IODINE SUPPLEMENTATION IN SWEDEN AND REGIONAL TRENDS IN THYROID CANCER INCIDENCE BY HISTOPATHOLOGIC TYPE

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We studied regional patterns of thyroid cancer incidence in relation to iodine intake and **iodinization** in Sweden using 5,838 incident cases diagnosed in the period 1958-1981. Region was defined either by iodine status, urban-rural status or **health-care** region (internal controls). Age, period and cohort models were fitted to evaluate trends and regional variation in incidence by **histopathologic** type. In iodine-deficient areas, the relative risk (RR) of developing thyroid cancer was 0.92 for all histologic types combined, 0.80 for papillary cancer and 0.87 for **anaplastic** carcinoma. Residence in iodine-deficient regions was associated with a 2-fold increased risk of **follicular** cancer in men (RR 1.98) and a 17% increase in risk in women (RR 1. 17). Regional differences in iodine intake fell after iodinization of the food supply, which was started in 1936 and enhanced in 1966. Nevertheless, incidence of both papillary and **follicular** carcinoma increased during the study period, with largely similar trends in iodine-deficient and iodine-sufficient areas. Overall, residence in urban or rural areas was not an important determinant of incidence, though trends in the incidence of papillary, **follicular** and **anaplastic** cancer did vary between urban and rural areas. The occurrence of thyroid cancer differed only marginally between the 6 health-care regions in Sweden, suggesting that the observations in regions defined by iodine intake were unlikely to be **artifactual.** Our data suggest that **iodinization** of the food supply is not associated with adverse trends in the occurrence of thyroid cancer.

Geographic and ethnic variations in the incidence of thyroid cancer are considerable. Regions of high incidence include Hawaii, Iceland, Kuwait and New Zealand, and there are large differences between ethnic groups in some of these areas. Filipinos in Hawaii, Pacific Polynesian Islanders in New Zealand and non-Kuwaitis in Kuwait show particularly high rates, and Filipinos in the United States also have higher rates than in the Philippines (Parkin ***et al.,*** 1993). Even in the Nordic countries, where standards of medical care, diagnostic practice, cancer registration and industrialization are closely similar, there is a 10-fold range in incidence of thyroid cancer. The highest overall rates are found in Iceland, with intermediate rates in Finland, Norway and Sweden, while the lowest rates are seen in Denmark (Fransilla ***et al.,*** 1981). Denmark has one of the lowest thyroid cancer incidence rates in the world. Geographical differences between the Nordic countries are most pronounced for papillary and medullary carcinomas of the thyroid, and they persist when cases first detected at autopsy are excluded to take account of different autopsy rates (Fransilla ***et al.,*** 1981).

Thyroid cancer incidence also varies widely within each of the Nordic countries (Jensen ***et al.,*** 1988). In Norway, the highest rates are observed in northern and coastal counties, and papillary carcinoma is twice as common in northern as in central counties (Thoresen ***et al.,*** 1986). In Sweden, for all histopathologic types combined, there are scattered regions of high incidence in southern and central counties (Jensen ***et al.,*** 1988).

The possible association between iodine intake and occurrence of the various types of thyroid cancer is controversial. Some authors have found an excess of anaplastic and follicular cancers in iodine-deficient areas (Heitz ***et al.,*** 1976; Bubenhofer and Hedinger, 1977; Harach ***et al.,*** 1985; Belfiore ***et al.,*** 1987), whereas papillary cancer seems to dominate in areas with a high natural iodine level (Fransilla ***et al.,*** 1981; Goodman ***et*** al., 1988). Although the highest follicular carcinoma incidence rates occur in Iceland and Hawaii, both iodine-rich volcanic areas, papillary cancer is still the most common type in these islands (Fransilla ***et al.,*** 1981; Goodman ***et al.,*** 1988).

An association between an increase in the iodine supply and a subsequent rise in the incidence of papillary cancer has been reported in several investigations (Heitz ***et al.,*** 1976; Hofstädter, 1980; Hedinger, 1981; Sambade, 1983; Harach ***et al., 1985;*** Rolon, 1986), but it remains unclear whether this reflects a causal relation.

Our aim was to define the regional distribution and time trends of the different histological types of thyroid cancer in Sweden during the period 1958-1981 as a way of evaluating the influence on thyroid cancer of the Swedish iodine supplementation program, which started in 1936 with limited measures but was reinforced in 1966 and 1971. Two other regional analyses were performed, using urban/rural residence and health-care region, respectively, as determinants of thyroid cancer incidence. No influence of health-care region on incidence would be expected, except insofar as these regions overlap with other regions, and these analyses were used as an informal control for the other analyses,

SUBJECTS AND METHODS

Study population

The Swedish Cancer Registry, established in 1958, receives compulsory notification of all cancer cases from the diagnosing clinician and the pathologist or cytologist. Coverage is considered to be close to 100%. Cancers for which the only evidence is a death certificate are not included in the Cancer Registry (National Board of Health and Welfare, 1984). A total of 6,935 cases of thyroid cancer were reported to the Registry during 1958–1981. After excluding 1,097 cases (15.8%) that were either first diagnosed at autopsy (704 cases, 10.2%), benign or not definitely malignant (330, 4.7%) or coding errors (63, 0.9%), a total of 5,838 (84%) primary thyroid malignancies were included in the study population (Pettersson ***et al., 1991).***

Sweden is divided into 24 counties; the population increased from 7.4 to 8.3 million during the study period. Three regional analyses were performed, based upon the patient's county of residence at diagnosis. In the first analysis, Sweden was divided into 2 zones, iodine-deficient (1.6 million population) and iodine-sufficient (6.7 million; Fig. ***la).*** These regions were defined on the basis of goiter prevalence in each county during the early 1930s and on more recent estimations of iodine intake and excretion. The second analysis was based on urban and rural areas, defined by population density (Fig. lb). The urban region (3.1 million) contains the 3 most populated cities

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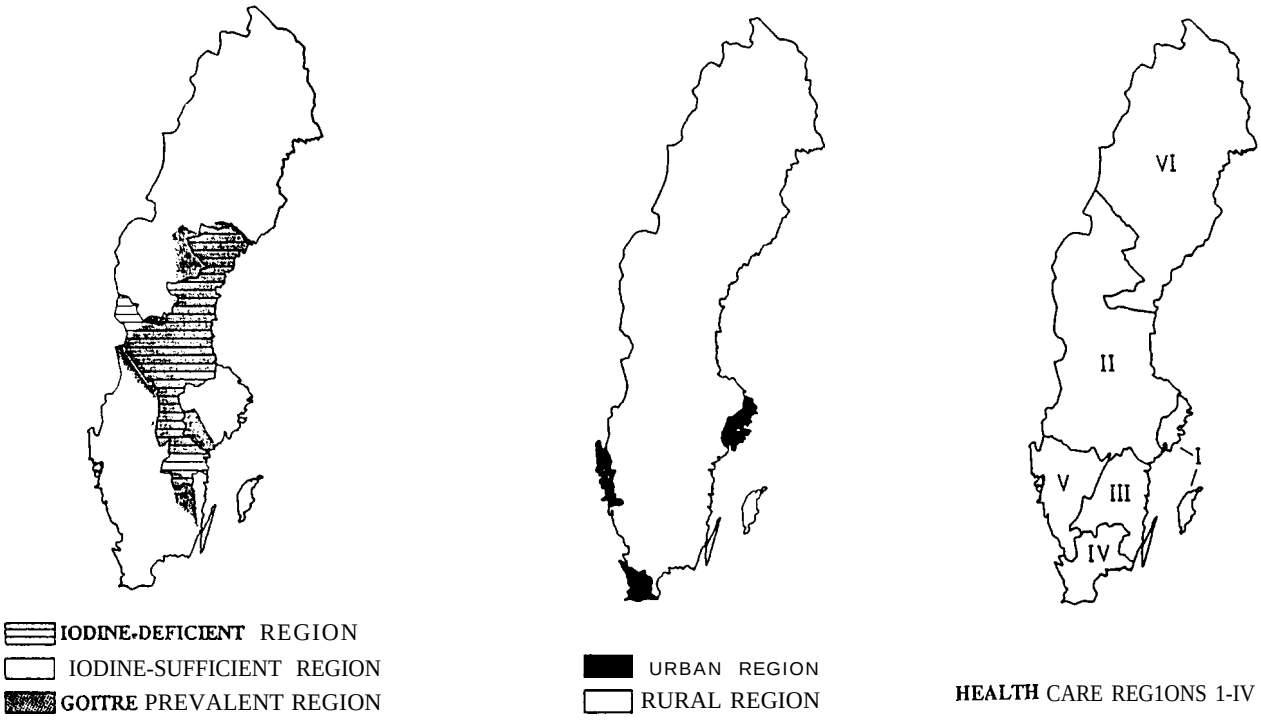

FIGURE 1 – Map of Sweden showing the 3 regional divisions used in this study. Left: Iodine-deficient region (1.5 million people) and iodine-sufficient region (6.7 million people), showing relation to the region of high goiter prevalence in the 1930s (shaded). Center: Urban (3.0 million people) and rural (5.2 million people) areas. Right: Health-care regions I-VI (0.9–1.8 million people per region).

(Stockholm, Gothenburg and Malmö) and their respective counties, while the rural region comprises the rest of Sweden, about 64% of the population (5.2 million). The iodine-deficient region defined here is wholly contained within the rural area. In the third analysis, incidence was examined separately for each of the 6 health-care regions, with populations between 0.9 and 1.8 million (Fig. 1*c*).

Accuracy of diagnosis

Uniform diagnostic criteria and similar availability and standard of medical care are important when performing regional comparisons of cancer incidence. The histopathologic classifications of thyroid cancer used in Sweden in the period 1958-1974 agreed well with the 1974 WHO on review of pathological slides (Helm *et al.*, 1980). Our own review of pathological material showed similarly good agreement over the longer period 1958–1981 for papillary (98%) and anaplastic (82%) carcinoma but lower concordance for follicular cancer (54% vs. 62%) (Pettersson ***et al.,*** 1991).

Classification of iodine intake

The national distribution of goiter prevalence in Sweden was investigated by Höijer (1931), who estimated that about 300,000 persons suffered from goiter at that time, with striking regional differences. Areas with a goiter prevalence exceeding 33% in women and 15% in men were denoted "goiter areas". Iodine supplementation was first given in the early 1930s to school-children in Sandviken, a town in the iodine-deficient area, where at that time no less than 65% of females aged 13 years suffered from goiter. In 1936, the National Board of Health recommended iodinization of salt (10 mg/kg) and the annual consumption of iodized salt rose sharply, increasing from 0.27 tons to 15 tons within 5 years in one of the cities (Falun) in the iodine-deficient region (Sjöberg and Sundlöf, 1971).

In 1961, however, the mean daily iodine intake of 85 μg from a typical Swedish diet (Sjöberg, 1978) was still considerably below the recommended dietary allowance of 150 μg (Food and Nutrition Board USA, 1989). Four years later, 30% of 1,000 consecutive medical patients in one hospital (Sundsvall) serving part of the iodine-deficient area still showed clinical evidence of goiter and 50% of 15–25 year olds had thyroid enlargement (Johnsson, 1965).

In 1966, the National Board of Health increased the recommended level of salt iodinization from 10 to 50 mg/kg. Only 3 years later, a further survey of the school-children in Sandviken found no difference in the prevalence of goiter compared to iodine-sufficient areas (Sjöberg and Sundlöf, 1971).

Increased iodine supplementation of cattle feed was introduced in 1971, milk being a major source of human iodine intake, especially in winter. In 1974, a survey in and around the city of Linköping (iodine-deficient area) showed that urinary excretion of iodine was still less than 40 μg/24 hr (normal range above 40 μg/24 hr) among those not ingesting seafood or milk, despite heavy iodine supplementation of both salt and cattle feed. Iodine content of water in the area was below 5 μg/l (Järnerot and Karlberg, 1974).

For this study, the iodine-deficient area was defined as those counties which overlapped most closely with the previous goiter areas (Fig. la), and the rest of Sweden was considered as iodine-sufficient. The distribution of cases by iodine region, sex, period of diagnosis and histologic type is shown in Table I.

Statistical methods

Annual incidence rates per 100,000 were calculated, with the Swedish population as denominator. Census data were available by sex, 5-year age group and county for 1960 and 1965 and for each year from 1969 onward (Statistics Sweden, 1961-1982). Incidence rates were standardized to the world

TABLE I – THYROID CANCER DIAGNOSED IN SWEDEN, 1958-1981: NUMBER OF CASES BY REGION, SEX AND PERIOD OF DIAGNOSIS

Category	Period of diagnosis					Total
	1958-1962	1963-1967	1968-1972	1973-1977	1978-1981	
Iodine-deficient						
Females	127	128	165	187	164	771
Males	54	56	69	82	49	310
Total	181	184	234	269	213	1,081
Iodine-sufficient						
Females	547	609	727	849	731	3,463
Males	193	234	286	311	270	1,294
Total	740	781	1,013	1,160	1,001	4,757
Urban						
Females	281	276	346	382	289	1,574
Males	81	102	130	130	109	552
Total	362	378	476	512	398	2,126
Rural						
Females	393	461	546	654	606	2,660
Males	166	188	225	263	210	1,052
Total	559	649	771	917	816	3,712

TABLE 11- THYROID CANCER DIAGNOSED IN SWEDEN 1958-1981, IN 1OD1NE-SUFF1CIENT (1S) AND IODINE-DEFICIENT (ID) AREAS: CUMULATIVE RATE FOR THE AGE-SPAN 0–74 YEARS AND TREND IN AGE-STANDARDIZED RATES (MEAN CHANGE PER 5-YEAR PERIOD) BY HISTOPATHOLOGIC TYPE AND SEX

Type	Sex	Number IS	Number ID	Cumulative rate (‰)		Trend (%)	
				IS	ID	IS	ID
Papillary	F	1,753	313	1.74	1.33	20*	22*
	M	538	116	0.55	0.47	18*	7
Follicular	F	947	259	0.91	1.04	6	14*
	M	332	94	0.35	0.42	3	21*
Anaplastic	F	509	150	0.42	0.52	−9*	−21*
	M	259	68	0.29	0.27	−18	−28*
All[1]	F	3,463	771	3.30	3.10	10*	12*
	M	1,294	310	1.36	1.31	11*	2

[1]Includes medullary cancer (n = 260) and cancers with unknown histologic type (n = 240). -*p <0.05.

population and cumulative rates per 1,000 (O–74 years) were calculated.

For multivariate analysis of age, sex, region, cohort and period, the data were organized into 15 quinary age groups (10-14 . ..80-84 years) and 5 calendar periods (1958-1962 . . . 1973–1977, 1978–1981). From these data, 5-year birth cohorts were constructed by combining age groups and calendar periods (1880-1884 . . . 1960–1964). The effects of age, sex, period of diagnosis, birth cohort and region of residence were investigated with age-period-cohort models on the assumption that the number of cases in each category was distributed as a Poisson variable, using a logarithmic link and the number of person-years in each age-period cell as the offset. Effects were assumed to be multiplicative, and the models were fitted with maximum likelihood methods using GLIM. To describe the trend in incidence rates, the approach of Clayton and Schifflers (1987*a*,*b*) was used. The goodness of fit of different models was assessed from the deviance, and the improvement in fit of successive models was evaluated using the change in deviance as a χ^2 on the relevant degrees of freedom. Trends in the age-standardized rate were calculated as the percentage change per 5-year period.

RESULTS

Overall results

The cumulative rate (O-74 years) for all thyroid cancers combined was slightly lower in iodine-deficient (Table II) and in rural (Table III) areas than in their respective reference regions. Age-standardized incidence for all thyroid cancer increased significantly over time in all areas and for both sexes,

TABLE III – THYROID CANCER DIAGNOSED IN SWEDEN 1958–1981, IN URBAN AND RURAL AREAS: CUMULATIVE RATE FOR THE AGE-SPAN 0–74 YEARS AND TREND IN AGE-STANDARDIZED RATES (MEAN CHANGE PER 5-YEAR PERIOD) BY HISTOPATHOLOGIC TYPE AND SEX

Type	Sex	Cumulative rate (‰)		Trend (%)	
		Urban	Rural	Urban	Rural
Papillary	F	1.83	1.56	14*	26*
	M	0.57	0.52	12	17*
Follicular	F	0.90	0.95	−9	13*
	M	0.41	0.35	−6	17*
Anaplastic	F	0.36	0.47	−14*	−8
	M	0.25	0.29	−18	−4
All[1]	F	3.34	3.21	3	14*
	M	1.39	1.33	8*	9*

'See footnote to Table II.–*p < 0.05.

with the exception of males in the iodine-deficient area and females in the urban area (Tables II, III). For each histologic type, the age distribution was similar in the 4 regions, though age-specific rates varied by region, especially for follicular and papillary cancer (Fig. 2). Medullary cancers are uncommon; they are included in overall rates, but separate regional analyses were not performed.

Iodine status

Papillary cancer. In both men and women, the incidence of papillary cancer was higher in the iodine-sufficient area than in the iodine-deficient area (Table II). Papillary cancer accounted for 48% of all thyroid cancers in the iodine-sufficient region and 40% in the iodine-deficient area. The cumulative

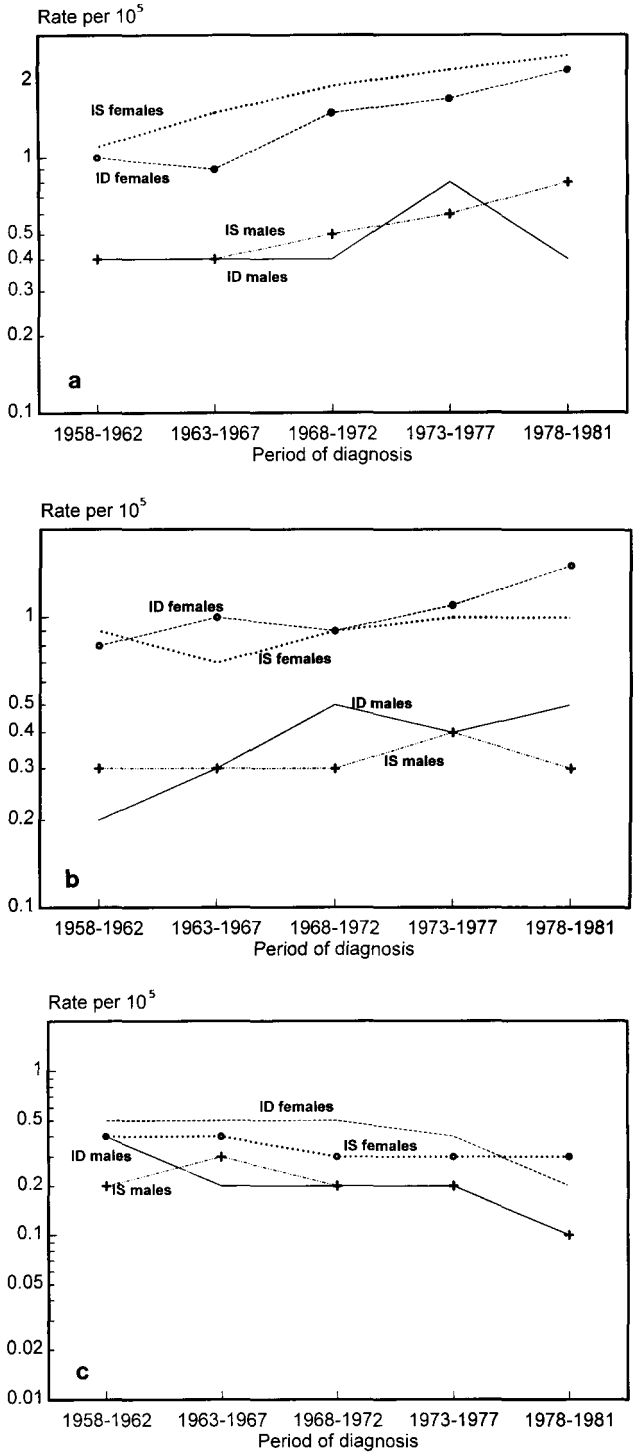

FIGURE 2 – Temporal trends in age-standardized incidence rates (ASR) for iodine-deficient (ID) + iodine-sufficient (IS) regions by sex, Sweden, 1958–1981. *(a)* Papillary cancer. *(b)* Follicular cancer. *(c)* Anaplastic cancer.

rate for papillary cancer in the iodine-deficient region was about 80% of that in the reference area. The age-standardized incidence of papillary cancer increased about 2-fold during the study period (Pettersson *et al.,* 1991). In the iodine-deficient area, there was a significant increase of 22% every 5 years among females and 7% (non-significant) among males. The corresponding increase in the iodine-sufficient area was about 20% every 5 years for both sexes (Table II).

Several models were fitted. There was a marked improvement in fit when sex, region (iodine status) and birth cohort were successively added to a baseline model including only age (Table IV). Inclusion of period of diagnosis and an interaction between sex and region did not significantly improve the model. The final model (model 4, Table IV) indicated that papillary cancer was 3 times more common in females than in males, increased substantially for successive birth cohorts (lO-fold for cohorts born after 1944 compared with the 1880-1884 cohort) and was lower in the iodine-deficient area. After adjustment for age, sex and birth cohort, the relative risk (RR) of developing papillary cancer for residents in the iodine-deficient area was significantly lower (RR 0.80; 95'% CI 0.73-0.88) than for residents in the reference area. The addition of calendar period to the model had no significant effect.

Follicular cancer. In both sexes, the incidence of follicular cancer was slightly higher in the iodine-deficient area than elsewhere. Follicular cancer accounted for 33% of all thyroid cancer in the iodine-deficient area compared with 27% elsewhere (Table II). Incidence increased for both sexes in all areas, but the trend was significant only in the iodine-deficient area, where the increase was 14% and 21% per 5-year period in females and males, respectively.

The fit of a baseline model including only age improved significantly when sex and region (iodine status) were included (Table IV). In contrast to papillary cancer, however, an interaction term for sex and iodine status was also highly significant (Pettersson *et al.,* 1991). Males in the iodine-deficient region had a 2-fold higher risk (RR 1.98; 95% CI 1.60–2.40) compared to males in the iodine-sufficient area, but for females this difference was only 17% (RR 1.17; 95% CI 1.04-1.32). The relative risk of developing follicular thyroid cancer for females compared to males was 1.8 in the iodine-deficient area and 3.1 in the iodine-sufficient area. Again, the addition of calendar period had little effect.

Anaplastic cancer. Anaplastic carcinoma accounted for 20% of all thyroid cancers in the iodine-deficient area and 16% elsewhere. Incidence fell in both areas during the study period, but the decrease was most rapid among males in the iodine-deficient area (28% every 5 years; Table II). The decline was more marked for males under 60 years of age and for females under 50.

Multivariate modeling revealed significant effects of sex and cohort but not of region (iodine status; $p = 0.07$). Addition of period of diagnosis and an interaction term for sex and region did not improve the fit (Table IV). Females had 1.7 (95% CI 1.5-1.9) times the risk of males in both areas, and the risk of developing an anaplastic cancer in the iodine-deficient area was 0.87 (95% CI 0.76–0.99) relative to that in the iodine-sufficient area.

Urban-fur-al differences

Papillary cancer. Papillary cancer accounted for 50% of all thyroid cancers in urban areas compared to 45 % in rural areas. Although cumulative rates were higher in urban areas, particularly for females, incidence increased rather more quickly in rural areas (26% and 17% every 5 years for females and males, respectively) than in urban areas (14% and 12%; Table III). In multivariate analyses, sex, region (urban/rural status) and cohort improved the fit of a baseline model (Table V).

Follicular cancer. Follicular cancer accounted for 27% of all thyroid cancers in the urban areas and 29% of the rural areas. Age-standardized rates fell slightly in the urban area over the study period but almost doubled in the rural area (Fig. ***3b).*** In multivariate analysis, age, sex and cohort gave the best fit, and

TABLE IV – EFFECT OF AGE, SEX, REGION (IODINE-DEFICIENT *VS.* IODINE-SUFFICIENT), BIRTH COHORT AND PERIOD OF DIAGNOSIS ON THYROID CANCER INCIDENCE BY HISTOLOGICAL TYPE

Model number	Terms in model	Compared with model	Deviance (change)	DF (change)	*p* value
Papillary carcinoma					
1	Age		1,288.1	285	
2	Age + sex	1	569.0 (718.5)	284 (1)	<0.001
3	Age + sex + region	2	549.79 (19.8)	283 (1)	<0.001
4[1]	Age + sex + region + cohort	3	346.96 (202.8)	265 (18)	<0.001
5	Age + sex + region + cohort + period	4	344.12 (2.9)	262 (3)	>0.25
6	Age + sex + region + cohort + sex*region	4	344.84 (2.1)	264 (1)	>0.25
Follicular carcinoma					
1	Age		806.44	285	
2	Age + sex	1	472.69 (333.8)	284 (1)	<0.001
3	Age + sex + region	2	446.82 (25.8)	283 (1)	<0.001
4	Age + sex + region + cohort	3	393.03 (53.8)	265 (18)	<0.001
5[1]	Age + sex + region + cohort + sex*region	4	376.06 (17.0)	264 (1)	<0.001
6	Age + sex + region + cohort + period	5	371.29 (4.8)	261 (3)	>0.1
Anaplastic carcinoma					
1	Age		336.70	285	
2	Age + sex	1	279.70 (57.0)	284 (1)	<0.001
3	Age + sex + region	2	276.40 (3.3)	283 (1)	<0.07
4[1]	Age + sex + region + cohort	3	228.55 (47.8)	265 (18)	<0.001
5	Age + sex + region + cohort	4	226.12 (2.4)	262 (3)	>0.25
6	Age + sex + region cohort + sex*region	4	227.05 (1.50)	264 (1)	>0.25

[1]Best-fitting model, under which relative risks cited in text were obtained.

addition of region (urban/rural status) had no effect on the risk (Table V).

Anaplastic cancer. Anaplastic cancer accounted for 14% of all thyroid cancer in urban areas and 19% in the rural area. Incidence in urban areas was slightly lower than in the rural area (Table III). In the urban area, incidence fell by half during 1958–1981 but changed very little in rural areas. A cohort model again provided the best fit, and urban /rural status had a significant effect (Table V).

Health-care region

Differences in age-standardized incidence of thyroid cancer between health-care regions were small, both for all histological types combined (0.9–1.2 per 100,000 for men and 2.7–3.3 per 100,000 for women) and for each individual type. The incidence of papillary cancer among females was slightly higher in regions IV (2.0 per 100,000) and VI (1.9 per 100,000; Fig. 1) than in other regions (1.5 per 100,000). Follicular cancer incidence was higher in females in region III (1.2 per 100,000) than in other areas (0.8 per 100,000). There were no obvious differences in the incidence of anaplastic carcinoma between the 6 health-care regions.

DISCUSSION

The role of iodine intake in thyroid carcinogenesis remains unclear. Several investigators have reported an association between iodinization and subsequent changes in thyroid cancer, an increase for papillary carcinoma and a decline for follicular and anaplastic carcinoma (Heitz *et al.,* 1976; Harach *et al.,* 1985; Rolon, 1986), but the theoretical grounds for associating iodine with carcinogenesis in the thyroid appear weak. The introduction of iodinization of the food supply might be expected to produce a period effect if all age groups were affected similarly or a cohort effect if the effect were limited to a critical age. Iodinization would also be expected, over time, to reduce the original differences in incidence patterns between the iodine-deficient and other regions.

Iodine supplementation was introduced in Sweden 1936 and again in 1966 by the addition of iodine to salt and in 1971 to milk *(via* cattle feed). We performed time trend and birth cohort analyses to identify any effect of changes in iodine intake on thyroid cancer incidence. Our observation that papillary cancer is more common in iodine-rich areas, whereas follicular cancer is more common in iodine-depleted areas, confirms previous reports (Williams *et al.*, 1977; Belfiore *et al.,* 1987); but overall thyroid cancer incidence was lower in iodine-deficient areas among both sexes, which contrasts with earlier findings of a positive association between endemic goiter and thyroid cancer (Cuello, 1969; Bubenhofer and Hedinger, 1977; Franceschi *et al.,* 1989).

In Switzerland, Argentina and Paraguay, iodinization of the food supply in areas of endemic goiter was followed by a rise in the incidence of papillary carcinoma and a reduction in follicular and anaplastic carcinoma within 20 years (Heitz *et al.,* 1976; Harach *et al.,* 1985; Rolon, 1986). In Sweden, the prevalence of goiter fell as expected following iodine supplementation (Johnsson, 1965; Sjöberg, 1972), but the subsequent trends in thyroid cancer were more complex. The incidence of papillary cancer rose steeply among successive birth cohorts born after iodine supplementation of the national food supply began, while the relative risk for follicular cancer fell in Sweden. There was no significant difference in the trends of papillary cancer incidence between iodine-deficient and iodine-rich areas, however. This suggests that the increase in papillary cancer was unrelated to iodine supplementation. Introduction of effective (goiter-preventive) iodine supplementation of the national food supply was associated with a greater increase in the incidence of follicular cancer in previously iodine-deficient areas than in iodine-rich areas.

TABLE V – EFFECTS OF AGE, SEX, REGION (URBAN *VS.* RURAL), BIRTH COHORT AND PERIOD OF DIAGNOSIS ON THYROID CANCER INCIDENCE BY HISTOLOGIC TYPE

Model number	Terms in model	Compared with model	Deviance (change)	DF (change)	*p* value
Papillary carcinoma					
1	Age		1,255.8	285	
2	Age + sex	1	537.20 (718.6)	284 (1)	<0.001
3	Age + sex + region	2	526.20 (11.1)	281 (1)	<0.001
4	Age + sex + region + cohort	3	323.18 (203.0)	265 (18)	<0.001
5	Age + sex + region + period	3	330.24 (196.0)	263 (21)	<0.001
6[1]	Age + sex + cohort	2	333.10 (204.0)	266 (18)	<0.001
7	Age + cohort + sex*region	6	321.15 (12.0)	264 (2)	<0.001
Follicular carcinoma					
1	Age		696.37	285	
2	Age + sex	1	362.62 (333.8)	284 (1)	<0.001
3	Age + sex + region	2	362.52 (0.1)	283.1	>0.1
4	Age + sex + region + cohort	3	309.43 (53.1)	265 (18)	<0.001
5	Age + sex + region + period	3	304.39 (58.1)	263 (20)	<0.001
6[1]	Age + sex + cohort	2	309.55 (53.1)	266 (18)	<0.001
7	Age + cohort + sex*region	2	307.13 (55.5)	264 (20)	<0.001
Anaplastic carcinoma					
1	Age		333.14	285	
2	Age + sex	1	276.16 (57.0)	284 (1)	<0.001
3	Age + sex + region	2	271.55 (4.6)	283 (1)	<0.03
4	Age + sex + region + cohort	3	223.75 (47.8)	265 (18)	<0.001
5	Age + sex + region + period	2	225.74 (50.4)	263 (21)	<0.001
6[1]	Age + sex + cohort	2	228.16 (48.0)	266 (18)	<0.001
7	Age + cohort + sex*region	6	223.14 (5.0)	264 (2)	<0.08

[1]Best-fitting model, under which relative risks cited in text were obtained.

Pathological classification of follicular cancer is notoriously difficult (Saxén *et al.,* 1978), and this is of particular concern when studying time trends (Fransilla et *al.,* 1981). A real increase in follicular carcinoma remains probable, however, since the effect of misclassification should have decreased over time. The usual misdiagnoses of follicular carcinoma arise from benign/atypical adenoma (excluded from this study), from goiter and from the fact that diagnostic criteria for follicular carcinoma have changed; about one-third of follicular carcinomas diagnosed before 1974 would now be assigned to papillary carcinoma (Hedinger and Sobin, 1974). The contribution to follicular carcinoma from misdiagnosed inflammatory goiter would also have vanished after the mid-1960s, and the true trend of follicular cancer is therefore likely to have been an even greater increase in iodine-deficient areas than was actually observed.

Anaplastic carcinoma decreased more markedly in the iodine-deficient region, where it was previously higher. Exclusion of less malignant conditions such as inflammatory goiter and small-cell lymphoma, some of which were previously misdiagnosed as anaplastic carcinoma, might have contributed to the decreasing incidence rates since the relative survival from anaplastic carcinoma has actually decreased over time (data not shown).

The incidence of papillary cancer was higher in urban than in rural areas, whereas that of follicular cancer in females and anaplastic cancer in both sexes was higher in rural areas. However, in comparison to the strong effects of age and sex and to the differences between areas defined by iodine status, the effect of urban/rural status was relatively small. Residence in urban and rural areas in Sweden had only a limited impact on thyroid cancer incidence patterns.

The absence of any clear effect of iodine supplementation on trends in papillary cancer of the thyroid does not confirm previous observations. Our study, however, has the advantage of comparable observations of the trends in areas both deficient and not deficient in iodine. It is possible that any effect of the iodine supplementation program occurred shortly after the first steps were taken in 1936 since the Swedish Cancer Registry was established in 1958. It is equally possible, however, that iodine deficiency is not, in fact, a risk factor for thyroid cancer at all, rather than that the increased prevalence of goiter caused by iodine deficiency simply increases the likelihood of thyroid cancer detection because of more frequent thyroid surgery.

In conclusion, we have shown substantial differences in the incidence of papillary and follicular carcinoma in regions of Sweden defined by iodine status. In contrast, no consistent differences were seen between urban and rural areas or between the 6 Swedish health-care regions. Our findings provide additional evidence that histologic type is important in understanding the etiology of thyroid cancer. High incidence of papillary carcinoma was observed in areas with adequate (goiter-preventive) levels of iodine, and follicular and anaplastic carcinoma were more common in iodine-deficient areas. In this respect, our observations fit with previous knowledge. The observed trends in incidence of papillary thyroid carcinoma do not suggest any adverse effect of iodinization since largely similar increases were seen in iodine-deficient and iodine-rich areas.

REFERENCES

BELFIORE, A., LA ROSA, G., PADOVA, G., SAVA, L., IPPOLITO, O. and VIGNERI, R., The frequency of cold thyroid nodules and thyroid malignancies in patients from an iodine-deficient area. Cancer, 60, 3096-3102 (1987).

BUBENHOFER, R. and HEDINGER, C., Schilddrüsenmalignome vor und nach Einführung der Jodsalzprophylaxe. *Schweiz. Wochenschr.,* 107, 733-741 (1977).

CLAYTON, D. and SCHIFFLERS, E., Models for temporal variation in cancer rates I: age-period-cohort models. *Stat. Med., 6,* 449–467 *(1987a).*

CLAYTON, D. and SCHIFFLERS, E., Models for temporal variation in cancer rates II: age-period-cohort models. *Stat. Med., 6, 469–481* (1987*b*).

CUELLO, C., CORRERA, P. and EISENBERG, H., Geographic pathology of thyroid carcinoma. *Cancer, 23,* 230–239 *(1969).*

FOOD and NUTRITION BOARD, *Recommended dietary allowances* (10th cd.), National Research Council, WashingtonD.C. (1989).

FRANCESCHI, S., FASSINA, A., TALAMINI, R., MAZZOLINI, A., VIANELLO, S., BIDOLI, E., SERRAINO, D. and LA VECCHIA, C., Risk factors for thyroid cancer in northern Italy. *Int. J. Epidemiol., 18,578-584 (1989).*

FRANSILLA, K., SAXÉN, E., TEPPO, L., BJARNASON, O., TULINIUS, H., NORMANN, T. and RINGERTZ, N., Incidence of different morphological types of thyroid cancer in the Nordic countries. *Acta pathol. microbiol. Scand. Sect A., 89,49-55* (1981).

GOODMAN, M.T., YOSHIZAWA, N. and KOLONEL, N., Descriptive epidemiology of thyroid cancer in Hawaii. *Cancer, 61, 1272–1281 (1988).*

HARACH, R. H., ESCALANTE, D., ONATIVIA, A., OUTES, J., DAY, S. and WILLIAMS, E., Thyroid carcinoma and thyroiditis in an endemic goiter region before and after iodine prophylaxis. *Acts Endocrinol., 108, 55-60 (1985).*

HEDINGER, C., Geographic pathology of thyroid disease. *Pathol. Res. Pratt.,* 171,285-292 (1981).

HEDINGER, C. and SOBIN, L. H., Histologic typing of thyroid tumours. *In: International histologic classification of tumours,* **11,** WHO, Geneva (1974).

HEITZ, P., MOSER, H. and STAUB, .1., A study of 573 thyroid tumours and 161 autopsy cases observed over a 31 year period. *Cancer,* 37, 2329-2337 (1976).

HOFSTADTER, F., Frequency and morphology of malignant thyroid tumours of the thyroid before and after the introduction of iodine-prophylaxis. *Virchows Arch. A Path. Anat. Histol., 385,263-270 (1980).*

HÖIJER, J. A., Kropfstudien. *Svenska Läkaresällskapets Handl., 57, 2-107 (1931).*

HOLM, L. E., LÖWHAGEN, T. and SILVERSWÄRD, C., The reliability of malignant th roid tumor diagnosis in Swedish cancer registry. *Acta pathol. microbiol. Scand.,* **88, 251-254(1980).**

JÄRNEROT, G. and KARLBERG, B. E., Jodbrist alltjämt en realitet? *Läkartidningen,* 71,1019-1021 (1974).

JENSEN, O. M., CARSTENSEN, B., GLATTRE, E., MALKER, B., PUKKALA, E. and TULINIUS, *H., Atlas of cancer incidence in the Nordic countries,* pp. 147–153, Nordic Cancer Union, Helsinki (1988).

JOHNSSON, S., Endemisk struma-frekvens i Medelpad. *Läkartidningen, 62,2049-2056 (1965).*

NATIONAL BOARD OF HEALTH and WELFARE, THE CANCER REGISTRY, *Cancer incidence in Sweden 1981,* Fritzes, Stockholm (1984).

PARKIN, D. M., MUIR, C. S., WHELAN, S. L., GAO, Y.T., FERLAY, J. and POWELL, J., *Cancer incidence in five continents,* Vol. VI, *IARC Scientific Publication 120,* International Agency for Research on Cancer, Lyon (1992).

PETTERSSON, B., ADAMI, H. O., WILANDER, E. and COLEMAN, M., Trends in thyroid cancer incidence in Sweden 1958-1981, by histopathologic type. *Int. J. Cancer, 48,28-33* (1991).

ROLON, P. A., Cancer de la thyroïde en zone de goitre endémique. *Ann. Pathol., 6,170-175 (1986).*

SAMBADE, M. C., High relative frequency of thyroid papillary carcinoma in northern Portugal. *Cancer, 51, 1754-1759 (1983).*

SAXEN, E., FRANSILLA, K., BJARNASON, O., NORMANN, T. and RINGERTZ, N., Observed variation in histologic classification of thyroid cancer. *Acts pathol. microbiol. Immunol. Scand. Sect. A, 86, 483-486 (1978).*

SJÖBERG, K. H., Strumasjukdomarnas profylax och behandling (Thesis). *Akad. avh. (1972).*

SJÖBERG, K. H., Jod och kosthåll. *Läkartidningen, 75, 2477-2479 (1978).*

SJÖBERG, K.H. and SUNDLÖF, G., Struma och jodprofylax. *Läkartidningen, 68,981-984 (1971).*

STATISTICS SWEDEN, *Publications for 1960 to 1981,* Liber, Stockholm (1961-1982).

THORESEN, S., GLATTRE, E. and JOHANSEN, A., Thyroideacancer i Norge 1970-1979 med histol typer och regional variation. *Tidsskrift for Norsk Laegeforen,* **31,** 2616-2620 (1986).

WILLIAMS, E. D., DONIAK, I., BJARNARSON, O. and MICHIE, W., Thyroid cancer in an iodine rich area. Cancer, 39,215-222 (1977).